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ROALD N. GRANT, M.D., *Editor*
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WARREN HENRY COLE, M.D.

Thirty-seven years ago, a young surgeon from Clay Center, Kansas developed a means for visualizing the gall bladder with X rays. Had Dr. Warren Cole never made another contribution to medicine, he would still have been assured immortality in medical history, for countless thousands of lives were and will be saved as a result of this scientific discovery.

In the years that have followed, Dr. Cole has turned to another challenging problem—cancer. Here, too, he is making a lasting impact in all three phases of the attack on cancer; namely, research, education, and service to the cancer victim. Whether his efforts are made in the operating room, at the bedside of the cancer victim, with his students and residents, or with volunteer workers in cancer, all gain inspiration as well as knowledge and skill in the fight against cancer.

1960 American Cancer Society Presidential Address*

Warren H. Cole, M.D.

FRIENDS AND MEMBERS of the American Cancer Society: As I stand here today in the closing months of this year of 1960 and the closing days of my sojourn as President of the American Cancer Society, I could question no man who might, in good conscience, ask, "Are the hopes of humankind, the cherished goal of civilization to conquer cancer nearer today than they were a year ago?" We, who are dedicated to the conquest of cancer, cannot limit these observations to the short space of a single year. We must go back a little further to the beginning and take a longer look at the changing scene.

Learning What Cancer Is

In the first efforts to learn what cancer is, scientists of a half century ago questioned whether or not it might be due to a microorganism. With knowledge of disease leaping forward, this idea was soon ruled out if, indeed, it had ever been seriously entertained. Cancer failed then to fill the prerequisites of an infectious disease and, indeed, it still does. Over the years, as the reservoir of facts slowly filled and the biologist and the chemist learned some of the fundamentals of the growth process, the means of mastering cancer's insidious propagation seemed almost insurmountable. But lurking in the wings of this continuing drama were some who still held to the idea that those mysterious virus molecules which seem half inanimate and half alive might hold the secret of cancer's beginnings. Then, as recently as 10 years ago, this theory had a resurgence of popularity, until today it is respected and pursued with vigor.

Meanwhile, a great many other avenues were being explored. Progress was slow. Eventually, however, some vastly important milestones in cancer research were passed. Achievements of such magnitude were made that they attracted four Nobel prizes in the last three years.

Only last year, two investigators in this country were made Nobel Laureates for their work in synthesizing RNA and DNA, the nucleic acids vitally involved in cellular reproduction. May I add that one of them received support from the American Cancer Society for many years, and also that the Society provided postdoctoral fellowships for the associates of the second Nobel prize winner.

Control Efforts

Even though the etiology of cancer proved not to be a rewarding field of investigation during earlier times, science pressed forward on other fronts with a vast assault to find chemicals which might control some forms of cancer. This search produced a trickle of substances which affected the cell. In the past decade, the number of compounds screened in the search for a possible chemical treatment has reached into the hundreds of thousands. From

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Professor and Head of the Department of Surgery, University of Illinois, College of Medicine, Chicago, Illinois.

**Abridged version of the address presented at the Biltmore Hotel, New York, October 26, 1960, during the annual meeting of the American Cancer Society.*

this wide spectrum, perhaps a score have been found which can be useful in human cancer. Strangely enough, one of the first, amethopterin, which was extensively used in treating leukemia for some years, now appears to be the first compound truly effective against a solid tumor. Known also by the trade name of methotrexate, this substance has apparently produced complete regression in a number of cases of choriocarcinoma in women.

This random search for chemicals has now given way to a more precise method of building molecules with certain qualities designed to attack the cellular growth processes through their enzyme pathways. Such an approach seems to be zeroing in on the target with much greater promise. As an example we might mention 5 FU (5-fluorouracil) which was developed by one of the Society's "lifetime" grantees, Charles Heidelberger of the University of Wisconsin, a man who is dedicating his entire career to cancer research. The importance of this work is that it has led to the development of a new type of chemical and a new means of attacking the cancer cell.

Another example of how promising chemicals are designed for a specific attack on the cancer cell are two compounds produced at Yale University by Arnold Welch. One of these, azauridine, is unique among chemotherapeutic agents as it appears to be nontoxic. Although enormous doses of the chemical are needed to affect the cancer cell, it appears to be a hopeful development, despite the present prohibitive cost of producing this compound.

New chemicals are appearing now almost on an assembly line basis. Although no one drug actually has produced a five-year cure of human cancer, many are useful, particularly in the leukemias, in extending by months and even years the lives of many of those who previously died within a few short weeks.

At my institution, we are obtaining some very encouraging data in our patients with cancer of the breast who are given nitrogen mustard at the time of operation to kill cancer cells dislodged from the tumor during operation and a short time previously. Over a period of four and one half years, we have so treated 60 patients, along with 60 control patients who have had radical mastectomy alone. In the control series, 15 patients have died of their cancer, whereas only six have died of cancer in the treated series.

However, in our colon and rectum series, we have observed no benefit from the procedure. This was to be expected since we were aware that certain drugs which are effective with one tumor are not effective with others. In a paper presented just two weeks ago at the meeting of the American College of Surgeons, the adjuvant committee of the National Institutes of Health, representing about 25 institutions, also reported favorable results with the use of adjuvant chemotherapeutic agents in cancer of the breast, but doubtful results in other tumors. In fact, their results with cancer of the breast utilizing thioTEPA instead of nitrogen mustard were superior to ours and so striking that we might expect the procedure to become a routine one in cancer of the breast in a few years if the figures of the two groups continue so favorably.

Great interest, too, is being shown in the techniques of perfusion and infusion of chemicals. This method of flooding the cancer area with cancer-killing chemicals permits heavy dosage without harm to other parts of the body. Rerouting the blood flow with use of the heart-lung machine spares normal tissues the toxic action of the drug. More-

over, it appears that we may soon be able to administer "antidotes" to the portion of the body outside the perfused area, thus still further minimizing the toxic action of the drug on the normal cells.

People, Numbers, and Causes

The laboratory approach is only one of many research assaults on the cancer problem that the Society supported with publicly contributed funds. Epidemiology is another approach. Indeed, one of the major purposes of the Society, as stated in the Society's Certificate of Incorporation, is "to investigate the conditions under which cancer is found and to compile statistics in regard thereto".

Most of our present knowledge of causes of human cancer have come from just such investigations. Just a year ago, in 1959, the Society launched its Cancer Prevention Study to learn, among other things, why some people may be more likely to get cancer than others. This is the largest statistical medical survey ever attempted in America and we would hope to learn from it not only how some cancers are caused but also ways by which they may be prevented.

Epidemiological studies have clearly proved that certain substances can cause cancer—how they cause it we still don't know—but the case against such carcinogens as occur in cigarette smoke is so strong that it seems certain now that some 20,000 lives a year are the cost the American public pays for this practice.

Those who would take comfort from the belief that scientists are not in agreement as to how cigarette tars and viruses might both be causes of neoplasms are being misled, for cancer appears to be a disease with multiple causes. Many virologists, firm in their theory that viruses are involved in human cancer, are nevertheless convinced that regular cigarette smokers are some 10 times more likely to get lung cancer than nonsmokers. Actually, there is no conflict between the two viewpoints. If it is demonstrated that viruses are a causative agent in lung cancer, the carcinogens in cigarette smoke will certainly be found to act in concert with them. The fact remains that today we have no means of eliminating the virus, even if it does exist, but there is a way that you can avoid the cigarette tar—remove the cigarette from your mouth.

Viruses, Vaccines, and Victory

The case for virology in cancer is growing. It has had some significant boosts in the past year. Most recently, teams at Roswell Park Memorial Cancer Institute and Sloan-Kettering Institute have found what most surely is a virus in specimens of human cancers. Previously, others had identified in photomicrographs what appeared to be virus particles. Still others have found a tumor-causing virus in certain types of animals. This virus leaps the species barrier, causing cancer to appear in another type.

If the answer to some cancers appears to be viruses, this does not necessarily mean that the fantastic course of seeking a Salk-like vaccine is the only goal. In pursuing investigations into immunity, we know that cancer may well respond to forces within the body, whether or not a virus is involved. Some of my own studies on spontaneous regression heightens this belief. We now have well-documented evidence of some 125 cases in which far advanced cancers seemed to cure themselves, at least temporarily. It seems apparent to me, that cancer, as far as the human system is concerned, becomes a foreign sub-

stance and that the body's defenses are mobilized against it, perhaps at some particular point in its wild course. What we need to learn therefore is how to mobilize this force when cancer strikes.

That this can be done is not beyond imagining. Some laboratory work supports the idea. A scientist at the Medical College of Virginia, Jerome Sacks, found that he could protect rats against any kind of induced cancer by first giving them a violent anemia with a viral agent he calls FHA for "filterable hemolytic anemia". At the Hektoen Institute for Medical Research in Chicago, a virologist, Steven Schwartz, protected mice from leukemia by injecting a serum prepared from volunteers who had been injected with a filtrate from brains of patients who died of leukemia.

I have mentioned the importance of the immune reaction as a hopeful area for further research, and I want to give this more than passing attention. It seems to me that here we have a most promising opportunity. If I am correct —and there are many scientists who will agree as to the promise of finally overcoming cancer through the development of a vaccine or a serum—we can well hasten this happy day if we set about it at once with renewed vigor and with strong emphasis in this direction.

Toward this end I am able to announce that the American Cancer Society has called a conference of experts in this field of immunology to be held next March. We expect that this meeting will bring together some of the best minds available on this subject. They are going to first take a look at the available facts, then they will sift them carefully for their significance and finally, they will discuss what is to be done and how to do it.

That More May Know And Fewer Need Die

Let us recall for a moment the vision of that little band of dedicated souls who founded the American Cancer Society in 1913. One of their goals was to alert the public to cancer and this has grown into a vast educational effort.

The record high cure rate of about one-third today may be attributable to professional education, better methods of treatment, better surgery, better supportive treatment and more effective radiation. One point that came out again and again at the Fourth National Cancer Conference last month was the fact that cancer, when diagnosed while local, and promptly treated, had a far better prognosis than when it had begun to spread.

It was impressively shown that the five-year survival rate of patients having their cancer diagnosed by detection examinations was much better than that of the group that had their cancer diagnosed in the routine way after symptoms had developed. In other words, it is clear that our public and professional education goal of earlier diagnosis is a sound one. In fact, I think we can say that a much greater effect in saving lives can be accomplished immediately through an expenditure of time, money and imagination in public and professional education than in any other aspect of our program.

More must be done against cancer through education because too often, indeed, eight to 10 months elapse before the patient gets to the physician for definitive treatment.

In one site we are making very good progress, cancer of the uterus, and when our new program aimed at cancer of the colon and rectum gets under way, we have high hopes for it. On the other hand, we are making only slight progress against cancer of the lung. If the

public could be converted to a willingness to think in terms of prevention of cancer of the lung, we might move ahead more rapidly.

Last year, at this time, the American Cancer Society Board of Directors passed a resolution calling for more research to learn why people do, or do not, take advantage of the means now available for protecting themselves against cancer.

The Society was urged to get the advice of behavioral scientists in planning research in public education. Also they were urged to launch studies to better understand the reasons for people's attitudes and actions on health. We know far too little about the factors which motivate men and women to seek medical help or why people delay in seeking medical aid. This is a major field that does, indeed, deserve greater emphasis than we have given it in the past. It is an area of research that should be explored.

Communications and Cancer

With the increasing flow of new medical approaches to the cancer problem it is vitally important that the physician on the firing line be constantly reinforced with information that can help him detect, diagnose and treat this disease in time. Moreover, the doctor needs to know not only what is new in clinical research but also what are some of the more promising areas of basic research. This problem of communications between the laboratory bench and the bedside will continue to grow as research expands its frontiers. Unless we are successful in improving these channels, the final solution to cancer will be unnecessarily delayed.

Now the other side of this matter is to bring the research worker closer to the clinical problem and the clinician. I make no claim for the originality of this idea, but its importance was stressed again at a meeting a few days ago of six men appointed to study mechanisms of payment for publication of scientific data in journals. All of us are aware of this tremendous gap between the clinician and research worker in cancer. Without question, we would be much more effective in the over-all program in the fight against cancer if our efforts—research and clinical—were better coordinated toward improvement in the welfare of the cancer patient, present and future. Accordingly, I hereby recommend the appointment of a committee, as soon as possible, to study mechanisms of improving co-ordination of effort in the clinical and research aspects of cancer for the benefit of the cancer patient.

The Scent and Sense of Triumph

As you know, I am a surgeon who has had intimate contact with cancer for more than 30 years. To think back three decades and consider the means we had at our disposal to control this disease then, and to compare it with the mighty forces arrayed against it today, leaves me with but one impression—that cancer cannot endure long as a major threat to human life.

What "long" is I cannot say, nor can any man with any degree of accuracy. But I do feel that the clues leading to the final solution may well be at hand. What we need is hope, energy and determination. What we need is courage to mount this attack in a direction and with the force that can only bring success. As your retiring president, I leave you this challenge.

Possible Diagnostic Implications in Cancer Research

Raymond F. Kaiser, M.D.

Generally speaking, the diagnosis of cancer at an early stage of the disease offers the most hope for successful treatment. This premise has excited the interest of numerous individuals in developing a diagnostic test for cancer. The result has been that hundreds of such tests have been proposed and reported in the medical literature. Evaluation of the majority of these so-called diagnostic tests has been carried out by a number of workers in the cancer field. I shall not attempt an exhaustive listing of these tests but suffice it to say that all of them have been thoroughly evaluated and none has been found satisfactory as a diagnostic test for cancer with the possible exception of the exfoliative cytologic technique.

Due to the rapid advances which have been made in medical and biological research during the last decade, methods, tools and procedures are at hand and are being developed which make possible micro-measurements of various blood, serum, urine and body fluid components which may reflect the presence of cancer. These circumstances have stimulated increased efforts to develop a laboratory approach to the problem of early recognition and diagnosis of human cancer. Several possible approaches to the problem are currently being explored. Six of these which seem to hold a measure of promise will be discussed in this paper—enzymes, blood proteins, hormones, immune reactions, cancer cells in the circulating blood, and the growth of cancer cells in tissue culture.

Chief, Diagnostic Research Branch, National Cancer Institute, National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare, Bethesda 14, Md.

Enzymes and Cancer Diagnosis

Enzymes govern the activities of cells. Under special circumstances, such as injury or disease, enzymes escape from the cell into the blood stream. While the mechanism by which this occurs is unknown, the fact of its occurrence in disease states has been substantiated by numerous investigators in the past several years. Investigations are currently under way to identify and measure enzymes in the blood and relate them to the growth of cancer in the body. This could provide the basis for a useful diagnostic test. In fact, some of these efforts have been successful: for example, urinary amylase and/or plasma lipase have been reported to be elevated in carcinoma of the pancreas; total plasma acid phosphatase is reported to be increased in breast carcinoma; plasma aldolase has been found increased in some prostatic carcinoma and may be elevated in about 20 to 25 per cent of cancer patients generally; plasma phosphohexoseisomerase has been found increased in some breast carcinomas and prostatic carcinomas; plasma phosphoglucomutase usually is increased in metastatic cancer; serum glutamic-oxalacetic transaminase and serum glutamic-pyruvic transaminase may both be increased in intrahepatic carcinoma; plasma glutathione reductase is increased in generalized carcinoma; 5-nucleotidase in the serum is elevated in

hepatic neoplasm; serum leucine aminopeptidase is elevated in cancer of the pancreas, ornithione carbamyl transferase in the serum is elevated in metastatic liver carcinoma and in some cases of cancer without metastases; and serum lactic dehydrogenase is increased in metastatic carcinoma, particularly of the central nervous system, in carcinoma and lymphoma involving serous surfaces and in myelogenous leukemia. While the findings just noted are not specific to cancer alone, they do indicate that, like other diseases, cancer produces chemical alterations in tissues, changes in enzymes, etc.

The last mentioned enzyme, lactic dehydrogenase, has attracted the interest of several investigators since in laboratory animals with fast-growing tumors there are indications of increased activity of the enzyme in the serum even before the occurrence of morphologic changes. This observation has been corroborated in experimental animals recently through the development of a procedure which permits the measurement of changes in plasma lactic dehydrogenase. At the same time it is reported that the new procedure has revealed the presence of a transmissible viral agent in all animal tumors thus far tested. Although this procedure has been limited to animals, it might provide a practical means for detection of a transmissible agent, if such exists, in human cancer and might yield a highly sensitive and specific diagnostic test. The findings of the LDH rise in animals with cancer seem to dovetail with recent reports by other workers in which markedly elevated LDH levels were found in many patients with overt cancers. These findings suggest that enzyme measurements may be useful in detecting fast-growing cancers in man.

What appears to be an important advance in the use of enzyme measurements for cancer diagnosis has been reported in the recent past. This involves a method for correlation of blood enzymes with the tissue from which they are released. Enzymes from various human tissues are prepared in purified or crystallized form and antibodies to them produced. These antibodies are then tested against the blood enzyme of unknown origin. The degree of reaction reveals the tissue of origin of the blood enzyme. If these findings can be substantiated and the procedure simplified it may hold great potential for a site-specific diagnostic test.

Since present methods of enzyme determination and analysis are time-consuming, procedures for carrying out these determinations by means of automation are being developed. The development of such methods will markedly speed the search for possible enzymatic changes associated with cancer. In spite of the incompleteness of current data on enzymes in cancer, it appears possible to forecast the emergence of patterns of enzyme assays which will be characteristic of the disease. In any event it seems reasonable to encourage investigation of the problem of cancer diagnosis using present-day enzymologic techniques.

Blood Proteins and Cancer Diagnosis

Throughout the years, numerous cancer diagnostic tests have been proposed, based on changes of one or more of the major components of the blood proteins. By and large, such changes as have been recognized to date are nonspecific for cancer. However, there have been some blood protein research findings on which there appears to be reasonable agreement in the literature —the albumin concentration decreases and the alpha globulins and fibrinogen are usually increased in the plasma of

patients suffering with cancer and that activity of a malignant tumor is generally reflected in the state of the plasma protein. (Rapidly growing highly malignant tumors produce different changes than slow-growing or relatively inactive tumors.)

Part of the difficulty involved in correlating plasma proteins and cancer is due to the complex and multiple nature of the various components and the lack of adequate techniques for separation and fractionation. Another difficulty insofar as early cancer diagnosis is concerned, is the problem of looking for a tiny increment of a particular component from a few cancer cells in the presence of the normal output from the masses of normal cells. Possibly, the search for a test would be more rewarding in the field of trace components where a qualitative all-or-none effect might be expected rather than in the field of one or more of the major components of the blood proteins.

Recent developments in research have made available newer techniques, such as gel diffusion, electrophoresis, chromatography, polarography and latex agglutination which are making it possible to sort out serum proteins. In fact, some 23 serum proteins are now identifiable in human serum with a definite hint that at least several of these may be further fractionated by refinement of existing techniques.

Although it is not known whether the mechanism of protein metabolism in tumor cells differs from that in normal cells, it is known that neoplastic cells contain abundant amounts of protein and possibly these excess amounts are reflected by increases in the tissue juices and eventually in blood plasma.

It appears to me that through the use of currently available techniques it is possible to isolate plasma proteins and it is highly probable that differences in the types of proteins may be found. If this can be substantiated, it may be that comparisons of serum protein profiles of cancerous and noncancerous individuals will reveal consistent differences in proteins which can be exploitable from a diagnostic point of view.

Hormones and Cancer Diagnosis

It is now becoming clear from the work of numerous researchers over the years that cancer growth, once considered to be wholly autonomous, may be profoundly influenced by many factors within the body of the host. Among these factors are the chemical products of the various endocrine glands—the hormones.

Considerable evidence appears to link steroid hormones with the cause and progress of cancer, even of cancer having no apparent relation to the sex organs and glands. For example, some forms of cancer tend to occur most frequently at times of life when hormone production is changing. This is particularly true at the menopause, and to a lesser extent at puberty. There are marked differences between the sexes in the occurrence rates of cancer within the same organ or tissues. Tissues under hormone control, such as breast, uterus and prostate, are commonly involved in the cancerous process. Tumors of the endocrine glands produce the hormones associated with these organs; e.g., steroid hormones and metabolites are elaborated in cancer of the adrenal cortex and ovary; adrenalin in pheochromocytoma of the adrenal medulla; insulin in pancreatic tumor; and gonadotrophin in chorio-epithelioma.

Cancer of the prostate or of the breast can sometimes be controlled for variable periods of time by the administration of hormones or the removal of hormone-producing glands. Several types of cancer can be produced in the

experimental animal through the administration of estrogens and the creation of other hormonal imbalances. Finally, there is the close molecular structural resemblance of the steroid hormones to methylcholanthrene, a chemical which causes cancer in almost every tissue it touches. All of the foregoing suggest strongly that the hormones play a significant and important role in the cancer process.

Much information is now available about the origin, production, progress through the body, use and excretion of hormones, which indicates that each human being has an individual pattern of hormone production and that deviations from this pattern may be associated with many types of disease including cancer. Such abnormalities of hormone production presumably precede by months or years any changes they may cause. Perhaps by study of the hormone patterns it may be possible to detect the tendency to the disease before signs and symptoms occur.

For the first time there are now available methods for the definition and measurement of a whole series of steroids produced and excreted in health and disease. As these techniques improve, disturbances in the excretion patterns can be related to disturbances in the manufacture, use and excretion of hormones by the body and these, in turn, to physical disease. Looking into the future, one can begin to see in these methods new possibilities for the diagnosis of cancer and other diseases.

Immunologic Approaches to Cancer Diagnosis

For many years investigators have wondered whether the presence of cancer in man stimulates the body's natural defense mechanisms in a manner similar to that which occurs in bacterial or virus infections, and if such defensive responses are evoked, could they be used to detect the disease. Interest in this area of cancer research is currently at a high level, possibly due to resurgence of the theory of the viral origin of cancer.

Considerable research has been and is being done on the immunologic reactions to cancer in man. Of recent interest has been a study in healthy human volunteers and advanced hospitalized cancer patients in which human cancer cells, grown outside the body, were implanted in the two groups of volunteers. Results of this study indicated that man does have a defense against cancer and possesses the ability to destroy implanted cancer cells removed from other human beings. In addition, the study indicated that the resistance to such cancer cells could be enhanced as was evidenced when the volunteers rejected a second implant much more vigorously after one injection of cells had been destroyed. The resistance evoked appeared to be partly specific for a particular type of cancer, but all types of cancer tested shared some common resistance-evoking factors. The same response was obtained when killed cancer cells were implanted. Whether the cancer cells contain a specific antigen which provokes this response cannot be answered on the basis of available evidence.

Numerous reported, so-called diagnostic tests have been based on an antigen-antibody reaction. Usually when these tests have been evaluated, they have been found lacking in specificity and usefulness. However, recently there has been reported an antigen-antibody test for multiple myeloma which is claimed to be able to detect the disease when other diagnostic methods fail.

If, indeed, a cancer-specific antigen could be demonstrated which is common to most or all cancer cells and not

shared by normal cells, the immunologic approach to cancer diagnosis would be established. A number of scientists are currently searching for such a substance. A great deal more work needs to be done before such a diagnostic tool becomes a reality.

Cancer Cells in the Circulating Blood

Numerous investigators have recognized tumor cells in the peripheral blood. Until recently, this phenomenon was considered an extremely rare event; however, current reports indicate that many cancer patients have circulating cancer cells. From our work it is believed that probably long before the tumor is clinically apparent, cancer cells are circulating in the blood stream, but their presence is not necessarily related to survival rates. For example, tumor cells are demonstrable in blood draining from the tumor in about 50 to 60 per cent of patients who undergo surgery. If these cells are a potential source of metastases, then obviously, there must exist in some patients an unknown means of control since metastatic spread often does not fit this pattern. Also when metastasis does occur, it is often a late, if not terminal, manifestation.

The full significance of these findings is not understood. Obviously, much more work needs to be done before conclusions can be drawn as to the significance of circulating cancer cells. With the data at hand, the usefulness of this observation in the field of cancer diagnosis is open to serious question. However, it may be that elucidation of this phenomenon will lead to a better understanding of the cancerous process in humans and possibly some of the factors which determine metastatic spread in internal cancers. Finally, it may be of considerable prognostic value.

Tissue Culture and Cancer Diagnosis

As tissue culture techniques have been improved and extended, the cultivation of human cancer cells by these methods has become a reality. Major efforts in this field have been directed toward getting the cells to grow by providing suitable media, adequate nutrients and appropriate environments. With the concentration of effort on development of suitable media for cell growth, the possibility of learning something about the development of cancer by studying the media has been essentially ignored. Thus, limited efforts have been directed toward investigation of metabolites of the cell as it grows in tissue culture. Studies of the biochemical and metabolic processes which take place in the media as a consequence of the presence of the growing cancer cell might result in findings for which determinations could be made in the human situation. It is timely to encourage such investigations, utilizing biopsy specimens, cancer cells in the blood and surgical specimens, so that a clue to the diagnosis of early cancer might be uncovered.

Summary

Although the majority of cancer tests which have been proposed and evaluated so far have not been found sensitive and specific enough for clinical use, the possibility of development of such tests seems hopeful. It is suggested that an open-minded attitude be maintained by those interested in the cancer problem since knowledge currently being accumulated in the several approaches commented on in this paper appears to hold real potential for contributing to improved cancer diagnosis in human beings. The cancer diagnostic field is one of intense interest and worthy of special effort.

Prognosis in Chronic Lymphocytic Leukemia

John S. Hirschboeck, M.D.

The serious implications of acute leukemia justify the feeling which most people have that its diagnosis portends an early and pathetic death. The more favorable prognosis of chronic leukemia often escapes the attention of physicians and laymen, and many do not realize that patients with chronic leukemia require a much different approach to the psychologic and therapeutic management of their illness.

That chronic lymphocytic leukemia may be particularly benign was emphasized by a panel of authorities[1] in 1955 in a symposium, the purpose of which was to recommend therapy. The consensus, with one dissenting opinion, was that many patients with chronic lymphocytic leukemia may enjoy a long, useful and comfortable life, even without resorting to radical and toxic therapy. In a study of 86 patients by Pisciotta and Hirschboeck, it was possible to observe 52 through the natural course of the disease. They observed that chronic lymphocytic leukemia fell into three well-marked categories: benign, aggressive and those complicated by auto-immune hemolytic anemia. Because of the differences in prognosis and therapy, it seems appropriate to enumerate those factors which characterize these three types of chronic lymphocytic leukemia and contribute to the prognostic outlook.

Age and Course

Chronic lymphocytic leukemia is a disease of old age. In a random series,[2] 85 per cent was known to occur past the age of 50, with males dominating about two to one. It thus further appears that the older the patient is at the time of initial detection of the disease the better his prognosis is.

Dean, School of Medicine, Marquette University, Milwaukee, Wisconsin.

Symptoms and Signs

Because of the high incidence of chronic lymphocytic leukemia in old age, the physician must decide which signs and symptoms may be attributed to leukemia itself, which are the result of certain of the complications of leukemia, and which, incidentally, are produced by the coincidental disorders which plague old age. In the series reported by Pisciotta and Hirschboeck, more than half of the patients had the diagnosis of chronic lymphocytic leukemia established by routine blood count, after they were admitted to the hospital for a totally unrelated clinical condition.

In the benign group, leukemia may be present without symptoms or signs such as splenomegaly or lymphadenopathy. The patient looks and feels well unless there is another disease present to account for symptoms. As time goes on, a few lymph nodes or the spleen may enlarge somewhat as the disease progresses slowly or not at all.

On the other hand, aggressive chronic lymphocytic leukemia behaves as a totally different disease. From the beginning, the patient is in difficulty and it is possible to date the onset of this disease more accurately. This form of chronic lymphocytic leukemia occurs in a younger age group and is frequently introduced by the appearance of painless, nontender lymph nodes, for no apparent reason. The most frequent site of enlarged lymph nodes is in the

neck, although the axillary, epitrochlear, mediastinal and inguinal nodes may also become enlarged, frequently more than one centimeter in diameter. It is often possible to see the nodes as a collar of tissue around the patient's neck. At times, lymphadenopathy becomes so extreme, that respiration becomes mechanically impaired. Together with or independent of lymphadenopathy, splenomegaly may occur, sometimes to a marked degree. As one follows a patient with aggressive leukemia over a period of time, the degree of progression in size of lymph nodes and spleen may be striking. Aggressive, chronic lymphocytic leukemia may also be accompanied by systemic complaints as fever, chills, night sweats, pruritus, weakness, malaise, fatigue, etc. Complaints referable to anemia are common, such as dyspnea, weakness and palpation of the heart. The patient appears sallow and chronically ill. Hemorrhagic manifestations such as purpura, ecchymoses and bleeding from mucous membranes often indicate a low platelet count. Other dermatologic manifestations such as maculopapular leukemic infiltrations of the skin and herpes zoster are not uncommon in the malignant variety of chronic lymphocytic leukemia. In addition, patients with this form of leukemia seem unusually susceptible to infection for two reasons. There is often a diminished number of granulocytes in the blood and the patient is deprived of their protective function. Also, insofar as lymphocytes have something to do with the synthesis of "immunologic" proteins, their abnormal growth may lead to an altered synthesis of gamma globulin resulting in hypogammaglobulinemia and an immunologic paralysis. All through the course of the "malignant" form of chronic lymphocytic leukemia, there may be difficulty in distinguishing leukemia from lymphosarcoma since features common to both diseases may be present.

Auto-immune hemolytic anemia may arise in any form of chronic lymphocytic leukemia, benign or malignant. Rosenthal, Pisciotta, Komminos, Goldenberg and Dameshek found that auto-immune hemolytic anemia could arise at any point in the course of chronic lymphocytic leukemia and that this may be the first clinical manifestation of illness. Of the various clinical signs associated with auto-immune hemolytic disease, splenomegaly was most frequent. The usual findings of hemolytic disease characterized this syndrome, such as pallor, icterus, profound anemia, reticulocytosis and a positive Coombs' antiglobulin reaction.

Blood Picture

In the typical "benign" form of chronic lymphocytic leukemia, there may be little or no anemia and no thrombocytopenia. In most cases, the leukocyte count is moderately elevated (under 80,000/cu. mm.) and remains so for the entire course. It is possible in certain patients to observe a normal leukocyte count and even a normal differential count. In this instance, a bone marrow biopsy would probably be the only means to establish the diagnosis of chronic lymphocytic leukemia. The characteristic thing about the blood picture of benign chronic lymphocytic leukemia is its remarkable stability over a period of years or its very slow progression.

In aggressive lymphocytic leukemia, anemia and thrombocytopenia are more often present than not. These are usually associated with involvement of the marrow by the leukemic process. The leukocyte count is often elevated and if no treatment is given, the white count may increase progressively. The

blood smear shows a predominance of mature appearing lymphocytes (monotonous blood picture). Clearly defined "blast" forms are unusual. This is the only type of leukemia in which immature cells do not appear in the peripheral blood. The predominant lymphocytes have very little cytoplasm, are quite fragile and are broken into "smudge" forms or "basket" cells when the blood smear is made. The marrow is packed with similar "mature" lymphocytes at times so tightly that a "dry" marrow tap may be experienced. In most cases of aggressive chronic lymphocytic leukemia, anemia has been attributed to suppression of erythropoiesis,[3] although in some cases, a decrease in erythrocyte survival time signifies an "occult" hemolytic process, even in the absence of reticulocytosis, spherocytosis, a positive antiglobulin reaction or any other of the overt manifestations of hemolysis.

Natural Course of Disease

It seems likely that the prognosis of chronic lymphocytic leukemia is best estimated by the behavior of the disease in the untreated state, as observed over a period of time. The length of survival of patients with this type of leukemia may be subject to considerable inaccuracy in estimation. On one hand, there is frequently difficulty with establishing time of onset of the disease. Onset of leukemia may be dated from the first appearance of symptoms or from the time the diagnosis is clearly established. Neither means is satisfactory in the "benign" form of lymphocytic leukemia because hematologic changes may exist for a variable period of time, without outward manifestations. The time of onset is more precisely dated in aggressive leukemia, because the actual symptoms of this disease are what cause the patient to seek medical advice. On the other end of the course, it may be difficult to decide the actual length of survival of patients with chronic lymphocytic leukemia because of the variable causes of death in the benign form. Cause of death in chronic lymphocytic leukemia may be due to an incidental disorder of old age. Of 54 deaths in chronic lymphocytic leukemia,[2] 20 were stated to be related to the leukemia, such as progressive lymphadenopathy, hepatosplenomegaly, wasting, hemorrhage, anemia, aplasia following myelo-suppressive therapy, etc. The remaining 34 died of conditions not directly related to leukemia, such as congestive heart failure, infection or malignancy. The increased incidence of carcinoma in chronic lymphocytic leukemia makes it advisable to watch for development of this disorder during the natural course of the blood disease. The best prognostic signposts and guides for therapy are, therefore, to be found in the changes that occur during the course of the disease itself.

A long remission may either occur spontaneously or after therapy. Reich has reported a case with no clinical or hematologic evidence of the disease during the last five years. The patient has complete freedom from any physical, blood or bone marrow abnormalities. The author speculates that perhaps some factor in the blood of one of the donors may have had a salutory effect on the outcome of the disease.

Therapy

To treat a blood count alone, with no regard for the needs of the patient or the rate of progression of the disease, sometimes results in greater harm than benefit. A great deal more is accomplished in recognizing the benign nature of most cases of chronic lymphocytic leukemia and adopting a "wait and see" attitude. In the average case,

it would be desirable to check the patient and his blood count every three or four months. More frequent examination, according to Dameshek,[1] would aggravate a leukemia "neurosis". During the period of observation, measures to rule out the occasional complications of chronic lymphocytic leukemia are in order. Auto-immune hemolytic anemia may be detected by the Coombs' antiglobulin reaction, the reticulocyte count and a serum bilirubin determination. Hypogammaglobulinemia may be determined by electrophoresis of serum proteins. If present, treatment with injection of human gamma globulin might be indicated.

Objective evidence for progression of leukemia is a clear-cut indication for treatment. This includes increase in size of lymph nodes, liver or spleen, progressive anemia, leukocytosis or thrombocytopenia. The choice of therapy is further dictated by the state of the disease. Localized masses of lymphoid tissue in the cervical, axillary and mediastinal area are best handled by irradiation to the area of involvement. A generalized disease with widespread involvement of lymphoid tissue, leukocytosis and systemic signs and symptoms is best handled by chemotherapy, such as chlorambucil or cytoxan® (Cyclophosphamide). Corticosteroids are indicated for auto-immune hemolytic anemia, thrombocytopenia, purpura and other forms of bone marrow suppression. Transfusions, particularly packed erythrocytes, may be administered only to maintain the hemoglobin at 10 grams per 100 ml. Gamma globulin may be administered as required in the event of hypogammaglobulinemia. Finally, all through the course, it seems well to remember that because of the age group affected, chronic lymphocytic leukemia is frequently accompanied by another degenerative or malignant disease, which may demand priority in treatment.

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Unproven Methods of Cancer Treatment

The following statement on Mucorhicin, a method of treatment proposed by the Drosnes-Lazenby Cancer Clinic of Pittsburgh, Pa., was recently distributed to the 60 Divisions of the American Cancer Society for their information.

Mucorhicin, the treatment used by the Drosnes-Lazenby Cancer Clinic in Pittsburgh, Pennsylvania, was developed by Philip L. Drosnes and Lillian M. Lazenby, some time between 1943 and 1948. Mr. Drosnes was reported to have been, prior to assuming the directorship of the Drosnes-Lazenby Cancer Clinic, a tire salesman in Pittsburgh. Mrs. Lazenby, associate director of the clinic, is reported to have previously been in charge of a hospital cafeteria. It is also said that her formal education did not extend beyond high school.

During the fall of 1948, Mr. Drosnes and Mrs. Lazenby were convicted of practicing medicine without a license and the clinic which they established in the basement of a church about a year before was closed. This sentence was later appealed and the case was thrown out for lack of evidence. The clinic was reopened in the fall of 1948 at its present address, 4774 Liberty Avenue, Pittsburgh, Pa., with Paul A. Murray, M.D. in charge of medical therapy. Joseph W. Wilson, M.D. joined Dr. Murray in 1949. Dr. Murray died in 1954; Dr. Wilson is now medical supervisor of the clinic.

Originally, Drosnes and Lazenby had both a test and a therapy for cancer. The test consisted of placing a drop of blood on a slide which was covered with tissue paper and oil silk and allowed to stand for 12 hours. Microscopic finding of diagnostic cell "A" was said to indicate cancer. Under the direction of a committee appointed by the Dean of the University of Pittsburgh School of Medicine, 20 specimens of blood were taken according to directions and submitted to the Drosnes-Lazenby Clinic for testing. Sixteen of the bloods submitted were duplicate specimens from eight apparently healthy laboratory workers. All 20 specimens were reported as giving positive tests. Since 1948, however, nothing has been heard concerning this test.

The name of the therapy, Mucorhicin, is derived from Mucor and Rhizopus, two fungi which are reported to have been found in analyses of specimens of the agent. This substance is said to be a substrate produced by the cultivation of a mold on a nutrient composed of yeast, salt, whole wheat and sterile water. The effective principle of the treatment is an exudate, or secretion, formed by this mold, which drips down into the substrate, or fluid beneath. The fluid, or Mucorhicin, is what is used in the treatment of cancer. In specimens of this agent examined in November 1948, varieties of fungi and some yeast, in addition to mites, debris, scales of unidentified insects, bacteria, acetic acid and water, were reported to be present. In specimens examined in March 1949 by the same laboratory, Rhizopus, Mucor and several species of Penicillium, but no mites, were found. Reports made to the Clinic of laboratory analyses of Mucorhicin in January 1954 indicated slight pituitary activity and androgenic activity, no estrogenic activity, and an appreciable amount of adrenal activity. According to Dr. Wilson in 1959, "Mucorhicin is designated

as an enzymatic product of biologically processed whole wheat grain and does not come under the classification of a drug." It is available to practitioners for "general practice at doctor's price of $6.75 per bottle, which is equivalent to a week's supply and is administered orally only in conjunction with a diet."

The "Drosnes-Lazenby Diet" allows considerable latitude among fruits and vegetables which may be cooked or uncooked, but must be fresh and preferably unpeeled. Beef, chicken, ham, lamb or veal and any fresh fish—boiled, broiled, roasted or baked—are allowed, but no fried meats and no fresh pork. Poultry and fish are preferable. Eggs, soft boiled or poached; bran, oatmeal or whole-wheat cereals with raw milk and dark brown sugar or molasses or pure honey; and buttermilk, weak coffee or tea, raw certified milk and gingerale are also allowed. Highly seasoned foods, pastries, rice, macaroni, spaghetti, noodles, and all wheat products unless made with "100% Whole Wheat Flour," should be avoided. Only country butter and unprocessed cheese may be used.

In 1955, it was reported that up to that time the Clinic had treated 1,900 cases, "most of them showing steady improvement, many seemingly well." At that time they were also treating arthritis, rheumatism and stomach ulcers with Mucorhicin.

The only known studies of response to the agent were performed in 1950 by the personnel of the clinic. Tissue examinations were done by a pathologist who later denied the claim that malignant tumors in rats were reduced 20-80%. He said that there was reduction in some and none or the reverse in others, but the differences were slight. A review of 15 case records by a recognized investigator who was told that these had been selected from 1,600 reports in 1953 showed that the basis for diagnosis did not always include tissue examination of either the original tumor or the alleged recurrence; X-ray or other therapy had been used in some cases; only two patients showed any improvement for which no other explanation was evident. In all but one case of 15, therapy had been initiated in 1950. The two cases with apparent favorable response must be considered in relation to the reported 1,600 that received treatment.

After careful study of the literature and other information available to it, the American Cancer Society has found no acceptable evidence that treatment with Mucorhicin results in any objective benefit in the treatment of cancer in humans.

NEWS and NOTES

● Physicians agree (three in every four) that all adults should have an annual checkup no matter how well they feel, and that all women should have a pelvic examination each year. They also agree (two out of three) that cigarette smoking is a major cause of lung cancer.

These are among the findings in a survey of the opinions and practices of a cross section of specialists and general practitioners in the United States made by the National Opinion Research Center of the University of Chicago for the American Cancer Society. The survey was made to determine the educational needs of physicians in cancer.

The study is based on 587 personal interviews with physicians, selected at random from a group of 5,000 previously sent questionnaires by the Society after patients had supplied their names as being their personal physicians.

Most physicians not only agree on the value of a regular health check-up, but two out of three recommend it to most of their patients. A similar proportion recommends such other protective actions against cancer as having an annual chest X ray (66 per cent), and for women, an annual pelvic examination (62 per cent) and monthly self examination of the breasts (71 per cent).

Vaginal smears are recommended to *most* women patients by 40 per cent of the physicians and to *some* women patients by another 42 per cent of the physicians.

To the question, "Is cigarette smoking a major cause of lung cancer?", 33 per cent answered "Definitely," 31 per cent "Probably," 13 per cent "Probably not," and nine per cent "Definitely not". The other 14 per cent expressed no opinion.

Only 43 per cent of the physicians smoked cigarettes regularly, and 5 per cent occasionally. Of the 29 per cent who used to smoke, a large majority have quit during the last nine years.

Twenty-two per cent of the physicians answered "No" to the question of whether all men over 45 should get annual chest X rays. One quarter of these gave as a reason their belief that radiation can be harmful. It is interesting to note that practically no one gave this reason in a similar study four years earlier.

In answer to the question, "Should adults get annual check-ups even if they feel well?", 74 per cent said "Yes," 11 per cent said "No," and 15 per cent said "It all depends."

Ninety-six per cent of the physicians have a hospital affiliation and 49 per cent of them practice in hospitals which have facilities for all five major cancer services—diagnosis, treatment, cytology laboratories, X-rays and registry.

A high proportion—93 per cent—approve the American Cancer Society's professional educational program for physicians, and 82 per cent approve its program of public education. Only 4

per cent of the physicians raised objections to the public education program—they felt that it arouses too much fear or exaggerates the danger. The great majority liked the program because it encourages earlier visits to doctors, educates people generally and teaches people cancer symptoms.

Half the physicians spend at least five hours a week reading medical journals. Practically all of them regularly read at least one journal. Twenty-six per cent of the general practitioners and 12 per cent of the specialists read the American Cancer Society's journal, *CA*, which is the second best-read journal—the *Journal of the American Medical Association* is first.

General practitioners spend, on an average, about a half-hour on a general physical examination; specialists take about 45 minutes. Specialists pay somewhat more attention than general practitioners to examining the rectum and female pelvis, testing blood and feces and giving chest X rays.

Very few of the physicians observe a 40-hour week. Three fourths of the nonspecialists work 50 or more hours a week; 43 per cent, 60 or more hours; and 20 per cent, 70 hours or longer. Only 6 per cent of the specialists work 70 or more hours a week, and about one half of them work 50 or more hours a week. Two thirds of the nonspecialists see more than 100 patients a week, and 20 per cent see more than 200. Almost half of the specialists see more than 100 patients a week, and 10 per cent see more than 200.

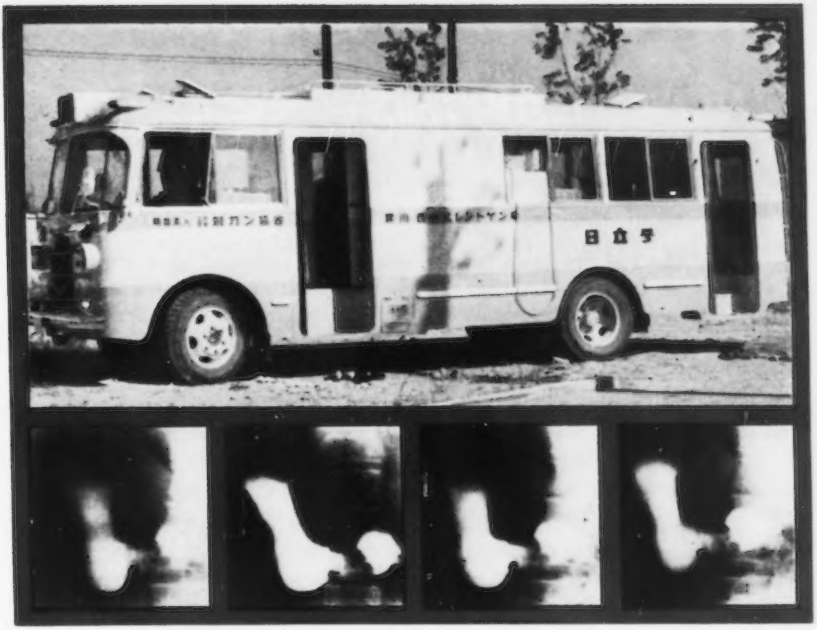
● The National Cancer Institute, through a survey, found that women have a better chance than men of living for five years after a diagnosis has been established of cancer of the tongue, thyroid and salivary glands, as well as in cases of melanoma and Hodgkin's disease.

According to Dr. Walter L. Mersheimer, cancer of the lung in women, if treatable surgically, also has a much better prognosis for five-year cure rates. The reason for this difference is unknown. However, the possibility that women usually seek medical aid sooner than men may be a factor.

● Substantial progress has been made in the American Cancer Society's program against uterine cancer through encouraging greater use of the cell examination for uterine cancer (Pap smear).

Started early in 1957, a 10-step program is now being actively pressed in all but one of the Society's 60 statewide and metropolitan Divisions. Over 750 local Units of the Society have programs. These Divisional programs are operating with the endorsement or active backing of state and county medical organizations. Thirty-one of the Divisions are providing fellowships for the training of cytotechnologists and 21 Divisions are helping to make available adequate laboratory facilities.

Professional information is being supplied to pathologists in 43 Divisions and to practitioners in 48 Divisions. The Society's film on this subject, TIME AND TWO WOMEN, has been shown over 30,000 times to a total audience of approximately 1,700,000 women. Over 300,000 young people have seen the Society's films on careers in medical technology. The American Cancer Society's professional educational film PELVIC EXAMINATION AND THE CYTOLOGIC METHOD has been seen by thousands of physicians and is proving a very useful educational tool for physicians.



● The pictures above illustrate the problem which cancer of the stomach represents to the Japanese in whom it is the leading cancer killer by far. The mobile photoradiofluorographic unit shown here is a desperate effort and is reminiscent of the fight against tuberculosis in the United States. The unit was developed at the Tohoku University, Sendai, Japan and reported upon at the International Union Against Cancer meetings in Tokyo on October 11, 1960, by Toshio Kurakawa, president of the university.

According to Kurakawa a mass screening survey of adults over 40 years of age is now under way. Each unit is capable of 150 examinations per day at an individual cost of 60 cents. Generally, four to six 35 mm films are taken in the abdominal, supine and half-prone positions. So far, according to Kurakawa, gastric cancer has been found in approximately 0.1 per cent of all examinees and gastric and duodenal ulcers in 0.8 per cent. [Photoradiofluorography for gastric cancer screening has not proved to be a practical procedure in this country.—ED.]

NOW HEAR THIS

"The last five cases in succession that I operated upon were inoperable. It makes you want to leave the operating room and weep. Gentlemen, we must do something to diagnose these cases earlier so we can cure them."

WHO: **Dr. Warren H. Cole,** Professor of Surgery, University of Illinois School of Medicine, President of the American Cancer Society.

WHERE: Hotel Biltmore, New York, N. Y. Oct. 28, 1960, Medical and Scientific Committee Meeting of the American Cancer Society Annual Meeting.

"In Russia we have 220 oncology centers, each with 100 beds where cancer detection, prevention and treatment takes place. Over 3½ million prophylactic cancer detection examinations were made in Russia last year. The detection team consisted of three doctors—a surgeon, oncologist, and internist or gynecologist in the case of women."

WHO: **Dr. Nicolai Blokhin,** President, Academy of Medical Sciences, USSR.

WHERE: Tokyo, Japan. Oct. 9, 1960. International Union Against Cancer Meeting.

"Now it is recognized that prostatic cancer is responsible for about 11,000 deaths annually in this country. The need for early diagnosis in cancer is nowhere more urgent than in prostatic cancer. I think equally as important as to urge men over 50 to see their doctors at least once a year is a recommendation that an educational program for physicians be instituted which should be concerned with proper technique of rectal examination. This should be carried out on a nation-wide basis."

WHO: **Dr. Herbert Brendler,** New York University Medical Center.

WHERE: Minneapolis, Minn. Sept. 15, 1960. Fourth National Cancer Conference.

"Professional reticence needs to be balanced against the public good. Much public reticence comes from public ignorance."

WHO: **Arthur Godfrey,** Entertainer.

WHERE: Biltmore Hotel, New York, N. Y. Oct. 27, 1960. American Cancer Society Annual Dinner.

"Heretical as it may seem to say it, in 1960, I believe we could make a more immediate and direct impression upon the cancer problem through agencies which will help us to detect presence of asymptomatic cancer, than if we knew actually what caused cancer. In other words, it takes time to appreciate and understand factors of etiology and to integrate that information usefully into management. Witness how long it took to absorb the full significance of the discovery of the tubercle bacillus into the therapy of tuberculosis. In time, of course, understanding the nature of a disease will have a far more penetrating effect upon the problem."

WHO: **Dr. Owen H. Wangensteen**, Professor and Chairman of the Department of Surgery, University of Minnesota School of Medicine.

WHERE: White Sulphur Springs, W. Va., Apr. 4, 1960. The 80th Annual Session of the American Surgical Association.

"Ladies and gentlemen, I am unhappy about this meeting. We have been warned away from my old friend tobacco. Last night we were fearfully warned away from alcohol. You would believe me justified in having some trepidations as to rising to speak about the female generative tract."

WHO: **Dr. John L. McKelvey**, Professor and Head of the Department of Obstetrics and Gynecology, University of Minnesota School of Medicine.

WHERE: Minneapolis, Minn. Sept. 15, 1960. Fourth National Cancer Conference Summary Session.

"Eight out of every nine detectable cancers of the rectum and colon will be missed if one depends on digital examination alone and does not make a habit of routine proctosigmoidoscopy. Cancer detection without a sigmoidoscope is like general practice without a stethoscope."

WHO: **Dr. Emerson Day**, Professor of Preventive Medicine, Sloan-Kettering Division, Cornell University Medical College.

WHERE: New York, N. Y. Dec. 15, 1960. Department of Preventive Medicine Staff Conference, Memorial Hospital for Cancer and Allied Diseases.

CANCER AROUND THE WORLD

Our Cooperation Will Benefit the Whole of Mankind*

By N. Blokhin

President of the USSR Academy of Medical Sciences

Cancer treatment, from my point of view, is one of the main problems facing medical science today. Despite the progress that medical science has made so far in the fight against many diseases and the increase in an average duration of man's life, there are quite a number of persons the world over who die of malignant tumors.

It is obvious to me and my colleagues in the Soviet Union that the successful solution of the majority of questions connected with the cancer problem is possible only by the united efforts of doctors, biologists, physicists, chemists, virologists, radiologists and some other specialists. Besides this the research will require that the laboratories be richly supplied with modern equipment.

All this makes imperative the creative contacts and cooperation of the scientists working on the cancer problem in various laboratories, cities and countries. In this regard, the Soviet-American agreement on scientific, technical and cultural exchange providing, in part, for cooperation in combating cancer is of great importance. We hope that this cooperation will be fruitful and will help mankind to learn as soon as possible the reasons for the main cancerous tumors in man and to develop effective methods of diagnoses and treatment of various forms of cancer.

The research data received during the last years suggest that new valuable materials on the mentioned problems will be obtained in the very near future. Scientists have already collected important materials on the role played by viruses in the formation of certain tumors in animals and the role of chemocancerogenic substances and ionizing radiations. There is certain progress in the development of treatment methods of a number of malignant tumors by hormones and chemotherapy. In various countries the methods of using isotopes are being developed and features characterizing the growth of the tumor studied. This is important for knowing the dependence of tumors on the various factors of the environment.

**Submitted by the Press Department of the Embassy of the Union of Soviet Socialist Republics, Washington, D. C.*

Much attention is paid to the cancer problem by such international organizations as the UNO and WHO. An active part is taken by the International Union Against Cancer which at present is preparing for the 8th International Cancer Congress to be held in 1962 in Moscow. In May 1960 we received leaders of the Union—Prof. Haddow from London, Dr. Dorn and Dr. Heller from the USA, Professor Mühlbock from Amsterdam—and discussed with them questions related to the preparations for the Congress. The Soviet oncologists know also the American scientists well from their meetings at different international conferences and visits to American scientific institutions.

I, too, have been in the USA several times and established contacts with the scientists working on the cancer problem. Remembering these meetings with great pleasure, I am convinced that the further broadening of our scientific cooperation will be very useful for the solution of the most difficult problems of cancer treatment. This will benefit the whole of mankind.

The Eighth International Cancer Congress will be held in Moscow, July 23-28, 1962. These meetings are held at four-year intervals. The Seventh International Cancer Congress was held in London, in 1958.

Lectures and papers will be presented, by simultaneous translation, in the working languages of the Congress—English, Russian and French.

Correspondence relating to the Congress should be addressed to the General Secretary of the National Organizing Committee of the U.S.S.R., Professor L. Shabad, Academy of Medical Sciences of the U.S.S.R., 14, Solyanka, Moscow.

Radical Mastectomy vs. Simple Mastectomy

[*The following editorials are reprinted by permission of* The American Surgeon. *Firor, W. M.: Regression in the treatment of mammary carcinoma. Am. Surgeon 26:63, Jan., 1960 and Crile, G., Jr.: A critique of Dr. Firor's editorial on breast cancer. Am. Surgeon 26:692-693, Oct., 1960.*—ED.]

Regression in the Treatment of Mammary Carcinoma

Progress in surgery does not always move steadily forward. There are times when it suffers regression. An instance of this occurred in the treatment of appendicitis in the years before the discovery of sulfanilamide, when the death rate rose steadily to 36 per 1000. During the past decade we have witnessed a similar deterioration in the treatment of mammary carcinoma. One cause for this is that the care of patients with this disease has been taken over by unskilled operators. The stimulus for this shift of patients came from McWhirter's teaching, that a simple mastectomy plus irradiation gives results which are as good as those following a radical mastectomy. With the prestige of the Edinburgh Infirmary behind this doctrine, and the substitution of an easy operation for a difficult one, it is not surprising that hundreds of doctors began to operate on their own patients instead of referring them to competent surgeons. Following their poorly executed operations the patients were usually referred for radiation therapy to a person inadequately trained.

What is even more distressing is that many competent surgeons, either out of pessimism over the results of their radical mastectomies or from misinterpretation of McWhirter's results, changed over to doing simple mastectomies. It is to surgeons in this group that this editorial is primarily directed. Let us look into the basis for their pessimism, and then into some facts about McWhirter's publications. Poor results following radical mastectomies are due to two causes: (1) operating on patients in whom the tumor is incurable; (2) whittling down the real Halsted procedure, either from ignorance, hurry, or sheer laziness. Haagensen has statistics to show that when these obstacles are overcome one can secure a 75 per cent 5-year survival rate in patients with axillary metastases of limited extent.

The late Dr. Barney Brooks went to Scotland to ascertain the basis for the dissatisfaction with the surgical treatment of mammary carcinoma. He found that the operations which were labeled "radical mastectomies" disregarded most of Halsted's principles and were not truly radical.

There are many competent surgeons who have followed McWhirter's lead without examining his work critically. Ackerman visited the Edinburgh Clinic and pointed out the following: 13 of the 719 patients did not have carcinoma; 220 of the patients had a concomitant bilateral oophorectomy. All of the patients in whom the disease persisted after irradiation were treated by an axillary dissection or by hormones. McWhirter's claim that radiation therapy destroys the malignant cells in lymph nodes has not been demonstrated; in fact, examination of his own material disproved this claim. Ackerman concluded, "He has presented no

objective evidence as to the necessity for simple mastectomy."

Even if McWhirter's thesis were correct, there are two practical problems which should deter most surgeons in the United States from following it; (1) there are insufficient well-trained radiotherapeutists; (2) there are many patients who cannot afford the time and the expense required for proper radiation therapy. It seems clear, then, that simple mastectomy plus irradiation should be reserved for the patients who are too feeble to undergo an extensive procedure and for those with incurable disease. The hard and deplorable fact is that many women with a mammary carcinoma which is curable by a Halsted mastectomy are denied their only chance of living by the substitution of a simple mastectomy and irradiation. This is indeed the reverse of progress.

WARFIELD M. FIROR, M.D.
1101 North Calvert St.
Baltimore 2, Maryland

A Critique of Dr. Firor's Editorial on Breast Cancer

As a surgeon with considerable experience with radical mastectomy and recently with simpler operations in the treatment of breast cancer I feel compelled to challenge Dr. Firor's editorial published in the January 1960 issue of The American Surgeon. My criticism is based on: (1) Dr. Firor's failure to document his assertions. (2) His personal attack on the motives of competent surgeons who employ simple mastectomy. I do not intend to argue the superiority of one or another method of treatment, but to point out that the issue is by no means settled and that clinical investigation of the results of various methods should not be discouraged.

Dr. Firor states that from the time appendectomy was first practiced until the discovery of sulfanilamide, the death rate from appendicitis rose steadily until it reached 36 per 100,000. He then states that during the past decades we have witnessed a similar deterioration in the treatment of mammary carcinoma. If there are statistics that bear out Dr. Firor's implication that the death rate per 100,000 from cancer of the breast has increased in the past 10 years, I have not been able to find them. The most remarkable feature of the natural history of breast cancer has been the constancy of its death rate, not only in the United States, but in all countries in which death rates are reported. McKinnon[1,2] has shown that these death rates appear to be unaltered, either by public education or availability of the most modern surgical and radiologic facilities.

Dr. Firor then states that amongst "competent surgeons" one of the causes for poor results following radical mastectomy is "whittling down the real Halsted procedure . . ." No data are given in support of this statement, and to my knowledge none exist. Meyer and Smith[3,5] report that the survival rate of patients operated upon for mammary carcinoma is not affected by the qualifications of the surgeon. I know of no report of a controlled series of cases in which modifications of Halsted's radical mastectomy have been shown to be less effective than the operation originally described. It would be strange if any operation devised more than half a century ago were still ideal.

In most fields we have seen progress; why not in the treatment of cancer of the breast?

It is surely true, as Dr. Firor points out, that a radical mastectomy is less time-consuming and less expensive than is simple mastectomy and radiation. This argument (even if it were valid) implies that all patients subjected to simple mastectomy must have radiation therapy, a point that is by no means established. Paterson and Russell's[4] studies in Manchester showed that radiation therapy after radical mastectomy contributed nothing to the survival rate of patients whose axillary nodes were involved. His studies also suggested that in cancers without nodal involvement, better results were obtained when the patients were not treated by radiation.

To add to the confusion, the few studies in which the stage of disease was comparable and in which the patients had been treated during the same period of time by different methods,[3,5,7] suggest a small, but definite superiority in the survival rate of patients who underwent simple operations as compared to those treated by radical ones. In my experience with simple mastectomy, which is now of only 5 years' duration, the increased survival rate after simple operations as compared to radical was evident in the favorable cancers without preoperative evidence of axillary spread. Most of these received no radiation therapy. When nodes were clinically involved, there was little or no difference in survival, regardless of the treatment employed.

It is now accepted that cancer cells are often distributed widely in the circulation and that the host's resistance appears to determine whether or not the circulating cells will implant and grow as metastases. Yet Dr. Firor states categorically, "The hard and deplorable fact is that many women with a mammary carcinoma which is curable by a Halsted mastectomy are denied their only chance of living by the substitution of a simple mastectomy and irradiation." In some cases this may be true, but in others it is possible that radical mastectomy may disseminate cancers that would not have metastasized after simpler operations. At present we cannot distinguish between the types of breast cancer that may be helped and those that may be harmed by radical operations.

Until we have learned how to recognize and to treat appropriately each of the various types of breast cancer, we should encourage competent surgeons to study new methods, ultraradical, ultraconservative, and combinations of these with other agents. Certainly the classic Halsted operation, which is neither radical nor conservative, is doomed to be partly replaced, either by more extensive regional lymphadenectomies or by simpler procedures. Few concepts in science or surgery are forever static. There is no reason why our concepts of breast surgery should be forever the same.

Dr. Firor, addressing himself to "competent surgeons", said that poor results are due to modifying the real Halsted procedure ". . . either from ignorance, hurry, or sheer laziness." It is hard to see how a competent surgeon could be accused of being ignorant of a technique so widely taught as the Halsted radical mastectomy. It is equally difficult for me to believe that "hurry" or "sheer laziness" motivates competent surgeons to perform operations that they recognize as inadequate. Such statements, unless documented by careful psychologic study of the motives of "competent surgeons," have the ring of emotionalism.

This comment is not written in defense of simple mastectomy nor of radiation therapy and it is not an attack on the Halsted radical mastectomy. These comments are written in defense of the "competent surgeons" whose motives Dr. Firor has attacked. It is also written in defense of the right of competent surgeons to engage in clinical research.

If surgeons wish to attack simple mastectomy and prove that it is not so good as the radical operation, let them document their articles with convincing proof. Until this has been presented, there is no need to criticize the motives of surgeons who perform simple mastectomies.

Dr. Firor, as a respected surgeon, should not try to stop the clock at the year 1900. He should do all he can to encourage clinical investigation.

GEORGE CRILE, JR., M.D.
Department of General Surgery
The Cleveland Clinic Foundation and
The Frank E. Bunts Educational Institute, Cleveland, Ohio.

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Errata

CA Bulletin of Cancer Progress, Volume 10, number 6, pages 191-192, November-December, 1960: In the article "Exfoliative Cytology of the Uterine Cervix and Vagina" by Leopold G. Koss, the figure numbers under the pictures do not correspond with the appropriate legends. The diagrams at right indicate the correct numbering.

Page 191		Page 192	
Fig. 1	Fig. 9	Fig. 5	Fig. 13
Fig. 2	Fig. 10	Fig. 6	Fig. 14
Fig. 3	Fig. 11	Fig. 7	Fig. 15
Fig. 4	Fig. 12	Fig. 8	Fig. 16

[*The following editorial is reprinted by permission of* Surgery, Gynecology & Obstetrics—*Copyright, 1960, by The Franklin H. Martin Memorial Foundation. Mueller, C. B.: Of cancer and viruses. Surg. Gynec. & Obst. 111: 635-636, Nov., 1960.*—ED.]

Of Cancer And Viruses

Cancer, as a disease entity, presents the most complex and difficult challenge which the surgeon is called upon to face. The mode, the vigor, design, and direction of attack upon this entity, either in the general or specific sense, are conditioned by our concept of the nature of this bizarre disease. The surgical and radiotherapeutic approach to cancer is predicated upon the assumption, supported by morphologic observation, that cancer is a disease of cells, that some cells in a local site undergo transformation into cancer cells, and that if extirpation of this local cell group is carried out the patient will survive. This concept implies a local transformation, presumably due to local influences, in which a cell goes awry, producing daughters that no longer obey or conform to the laws of the body, thus demonstrating autonomy. These cells produce local phenomena by cellular proliferation and distant phenomena by cellular migration and implantation. The properties of proliferation and migration are properties of cells that respond to the stimulus of inflammation, such as the histiocytes, leucocytes, macrophages, and plasma cells. During recent years, some interest has been shown in the idea that neoplasia, in general, represents a type of cellular response to some inciting agent in a manner somewhat resembling the cellular response to any inflammatory stimulus.

The recent demonstrations of the relationship between smoking and lung cancer have subtly implied that an agent in the smoke alters the bronchial epithelium in such a way as to promote the proliferation and migration of epithelial cells. This has been the latest in a long series of observations relating the origin of human and animal cancers to a presumably specific agent. It is probably not too far afield to state that most workers believe there are one or more agents which, when introduced into a receptive cell, will cause that cell to undergo changes characteristic of cancer. Tumors in chimney sweeps, aniline dye workers, Schneeberg cobalt miners and American smokers have been cited as examples of chemical carcinogen activity. However, none of these clinical examples, and few of the chemical carcinogen experimental cancers, have shed light upon the genetic, biochemical, or enzymatic alterations which have led directly to cancerous activity. Currently, the most acceptable thesis states that normal cells undergo transformation to autonomous malignant cells, but in laboratory animals, most autonomous tumors develop from pre-existing dependent tumors or precancerous lesions, and it is not beyond the realm of possibility that the same may eventually be noted to be true for human cancers. Should this become a fact, our thinking may have to be reoriented toward the possibility that chemical carcinogens may merely alter the recipient cell and thus make it susceptible to an agent which is able to cause genetic and somatic mutations which are transmissible to the daughter cells. It goes without saying that whatever imprint is made upon the original cell during its transformation must be transmitted through many generations. This transmission may be

affected by an original genetic mutation that breeds true, or by nuclearsomatic transmission of the agent, or the agent's offspring, to the cellular offspring. The latter possibility, of course, suggests infestation with an agent such as a virus.

There has been fairly conclusive evidence that in experimental animals, a few cancers have viruses as their etiologic agent—mouse leukemia, rabbit papillomatosis, chicken sarcoma, mouse mammary tumor, frog renal carcinoma, and the multiple organ tumors caused by the mouse polyoma virus, to mention a few. These tumors have yielded the information that cancer viruses are not always similar to each other. The Rous sarcoma virus contains nucleic acid of the ribose type (RNA) while the Shope papilloma virus contains nucleic acid of the deoxyribose type (DNA). By using fluorescent antibodies, it has been possible to demonstrate that the mature virus is present only in the keratinizing (old) papillomatous cells in the rabbit papilloma, implying that in the young daughter cells the virus is present in an immature form. It seems reasonable to expect that some human cancers will soon be proved to be due to viral infestation. Dmochowski has identified virus particles in human leukemia; Fortner has produced bile duct cancer in hamsters with human bile; Grace has produced malignant tumors in mice by cell-free extracts from human tumors; Powers has induced hyperplasia in hamsters by cell-free extracts from the sputa of patients with pulmonary cancer, and Mueller, Menefee, and Ivler have observed virus-like particles in human colon cancer.

The method of establishing that any viruses recovered from human cancer have etiologic relationship to that cancer is bound to be extremely tedious. At present there is no good description of the morphologic response of a cell to the presence of tumor viruses. Grossly, it is possible to note that cell proliferation and migration occur, and this effect can be noted in the whole animal. Microscopically, there has been no consistent intracellular response to the presence of these viruses and such response, if any occurs, should be observable. Ordinarily we conceive of the use of Koch's postulates when thinking of the identification of bacteria as etiologic agents for disease, and such orientation has been brought into the infectious virus field. Such opportunities to test the carcinogenic activity of suspected human tumor viruses will be difficult to get, and methods other than human experimentation will have to be devised in order to obtain the required information.

Should the viral etiology of some human cancers be established, its importance to the surgeon is difficult to assess. Such an etiology may well suggest that cancer is a systemic disease, whose local manifestations occur because local trauma at the cellular level has set the stage. A precancerous state may thus be a prerequisite to the development of cancer, and if this proves to be true, our attention may well be directed toward extirpation of all such precancerous states, rather than toward antiviral therapy of established disease.

C. BARBER MUELLER, M.D., F.A.C.S.

Looking at Cancer

A commentary on the Jan.-Feb., 1961 issue of CANCER, a journal of the American Cancer Society, Inc.

John W. Berg, M.D.
Associate Editor, Cancer

Merrill and Ross report on the treatment of vulvar cancer on the basis of 83 primary cases. Excisions less than radical vulvectomy seemed too conservative. Node metastases were found in 37% of the patients. More than half included contralateral involvement; deep nodes were often involved even when the superficial were not. The authors thus conclude that among node dissections bilateral removal of both superficial and deep nodes is best. However, they do not give this most radical of operations a blanket endorsement, because of the frequency of major postoperative complications. They still recommend tailoring the operation to the patient.

Pinkel reports that chlorambucil seemed of definite value in producing remissions in childhood lymphoma, but that only spotty effects resulted from its use in other neoplasms of children. Vaitkevicius et al. report on 5-fluorouracil and find it especially valuable for colon and liver cancer; for these diseases it seemed better than the radiomimetic drugs. Patients with breast and ovary cancer also were helped. As in most series, good results could be obtained only when the drug was given to toxicity. With careful patient management all such toxic effects were controlled and temporary.

McGavran et al. believe that laryngeal cancers can be classified preoperatively into those with low or high chances of having node metastases. Small cancers spread to nodes frequently when they lie directly on the cords. Above or below the cords, only the larger tumors were associated with a substantial number of positive nodes. Microscopically they found a high rate (48%) of bilateral metastases when only one side of the neck was clinically positive, suggesting that bilateral neck dissection may be the operation of choice in these cases.

Tellem et al. try to clarify the arguments about how many single thyroid nodules really are cancerous. First, they make clear that the thyroids operated upon are not representative of thyroids as a whole, but are selected because some abnormality has aroused a doctor's interest. Second, clinical guesses that nodules were single weren't completely accurate: one fifth of the supposedly single nodules proved multiple on pathological examination. Because of this inaccuracy the authors had the same 13% incidence of cancer in surgically selected thyroids, regardless of whether one or more than one nodule could be felt. It was only when the pathologist counted nodules that single tumors proved more dangerous—18% were malignant, as opposed to 6% in other glands. Clinical judgment was the best guide to thyroid cancer; two thirds of really suspicious thyroids were found to contain cancer, compared to only 9% of the rest. Age and sex selection were of some help; scanning for I^{131} content was the best single aid since 12 of 14 malignant nodules studied had reduced I^{131} uptake.

Wilson and Anderson observed in physical examinations of over 1000 people that about 20% had plantar and palmar nevi. They have calculated from this and from the known frequency of melanoma in these sites that the chance of any one of these nevi becoming malignant is only 0.018%, or less than one chance in 5000. Adequate removal is not simple and they recommend aggressive surgery only for a suspicious or changing lesion, not for a benign-looking mole just because it is on the palm or sole.

Sholiton et al. confirm previous findings that lung carcinoma, unlike most cancers, is associated with adrenal cortical hyperplasia.

Weiss and Ingram provide convincing histological, chemical and clinical evidence that the 80% of bronchial "adenomas" which look like carcinoids *are* carcinoids and no more benign than their intestinal counterparts.

Rotkin reports that even with sensitive tests he can find no clear hereditary factor in cervix cancer.

Keeping up

Cervical Carcinoma in Negro Women

Christopherson and Parker studied 10,045 women (5,882 were Negro; 4,163, Caucasian) by routine cervical studies at the Louisville General Hospital.

There were no significant socio-economic differences between the groups. Previously reported studies suggested a much higher incidence of carcinoma of the cervix in Negro women. However, in this study, the finding was not confirmed and even suggests a higher incidence of carcinoma of the cervix in Caucasian women of comparable backgrounds.

Christopherson, W. M., and Parker, J. E.: A study of the relative frequency of carcinoma of the cervix in the negro. Cancer 13:711-713, July-Aug., 1960.

Interrelationship of Pregnancy and Melanoma

A number of medical reports have covered the relationship of pregnancy and melanoma; the findings have been that there is either an acceleration of the progress of the disease or a remission. Case reports of a total of 413 females with melanoma of the authors' series were reviewed. Lesions of the eye, mucous membranes and perianal regions were excluded. One hundred and fifteen pregnant females were compared with a control group of 141 nonpregnant women of child-bearing age. The authors concluded that there was no difference in prognosis of either group as measured by rapid and/or generalized spread of the disease. Five and 10-year survival rates were respectively 47 and 42 per cent in both groups. Surgical treatment during pregnancy, as in the nonpregnant person with melanoma, is indicated.

George, P. A.; Fortner, J. G., and Pack, G. T.: Melanoma with pregnancy; a report of 115 cases. Cancer 13:854-859, July-Aug., 1960.

Peptic Ulcer and Endocrine Tumors

A review is made of 101 patients with peptic ulcer who had an associated adenoma and/or hyperplasia of the pituitary, pancreas, adrenal glands, parathyroid glands, alone or in combination. The incidence of lesions involving the parathyroids and pancreas was slightly higher than of those involving the other glands. This may be related to pathological technique. The only malignant tumors were noted in the pancreas. Hyperinsulism was noted in less than one-half of all tumors. The authors feel that the Zollinger-Ellison syndrome should include more than the original description of extreme gastric hypersecretion, peptic ulceration, and a non-insulin producing islet-tumor of the pancreas. They believe that this symptom complex of endocrine gland lesions and peptic ulceration should include extreme gastric hypersecretion, peptic ulceration, diarrhea at times resulting in a malabsorption syndrome, multiple adenomas and/or hyperplasia

(either alone or in combination) involving the pituitary, pancreas, parathyroids and adrenals. Because of the parasympathomimetic effects of all of these tumors it still remains questionable whether or not these tumors in themselves are ulcerogenic. No patients have been cured of their ulcer by having only the tumor removed. Cures have resulted only when associated gastrectomy was undertaken.

Murphy, R. T.; Goodsitt, E.; Morales, H., and Bilton, J. L.: Peptic ulceration with associated endocrine tumors. Am. J. Surg. 100:764-778, Nov., 1960.

Breast Tumor in Adolescent Females

This report and discussion of two cases of large breast tumors in adolescent females emphasizes the relationship of giant fibroadenoma, cystosarcoma phyllodes and virginal hypertrophy of the breast in adolescent girls. The first two conditions are closely related and the third (virginal hypertrophy) has been confused with fibroadenoma by the clinician. Histologically, the resemblance between virginal hypertrophy and fibroadenoma is so marked that the pathologist may not be able to distinguish between the two. The author believes that in adolescent females these three conditions may be a different manifestation of a common stimulus—the excessive production of estrogenic hormones. Local excision is believed safe even in the case of cystosarcoma phyllodes since, to the author's knowledge, there has been no instance of metastases from this large breast tumor in adolescent girls. However, there is a difference in the behavior of cystosarcoma in adolescents from that in adults. In adolescents the tumor grows rapidly over a period of a few months while, in middle age, cystosarcomas appear after having grown slowly from a pre-existing fibroadenoma. Also, in adolescents, cyst formation and cutaneous ulceration do not follow, nor do metastases occur.

Wulsin, J. H.: Large breast tumors in adolescent females. Ann. Surg. 152:151-159; July, 1960.

Osteogenic Sarcoma in Children

A review was made of results of treatment of 129 children under the age of 16 who had osteogenic sarcoma. There were more females in the series than males, which is not consistent with the sex distribution in adults. All cases were diagnosed by biopsy at the Mayo Clinic between 1909 and 1958. Lesions usually involved the metaphysial end of long bones. One hundred and five patients (81.4%) had tumors that arose in the bones of the lower extremities. Of these, 88 (68.2%) had tumors about the knees; 13 (10.1%) had tumors involving the upper extremities, whereas only 11 (8.5%) had tumors that arose from other bones of the body. Symptomatology consisted of pain, warmth, tenderness, redness, limitation of motion of

the joint adjacent to the tumor, as well as signs and symptoms of metastatic disease, especially in the lungs. Amputation, using two tourniquets proximal to the tumor was the treatment of choice. One-hundred and one of 122 patients had amputations. Of 22 patients who survived five years or more, 21 of them had been treated by amputation. None of the patients treated by local excision of the tumor and radiation survived five years. One girl survived 34 years after receiving only radiation treatment. The five- and 10-year survival rates were 22.2 per cent and 19.5 per cent respectively. The rates are comparable to those of patients of all ages reported elsewhere and tend to correct the erroneous concept that prognosis is very bad in children with this condition. Two factors besides amputation seem to modify survival prognosis. These are: (1) the less the degree of anaplasia of the tumor, the better the prognosis; (2) it seems that patients with lesions most suitable to radical surgical treatment, e. g., lesions of the tibia as contrasted to the femur, have better survival rates. Although disfigurement and certain psychological reactions may occur, survival justifies amputation and assures relief of pain.

Hayles, A. B.; Dahlin, D. C., and Coventry, M. B.: Osteogenic sarcoma in children. J.A.M.A. 174:1174-1177, Oct. 29, 1960.

Carcinoma in Situ of the Uterine Cervix

Histologic and topographic studies have been made on 52 cone biopsies of the cervix containing carcinoma in situ and 11 cases of atypical hyperplasia. Carcinoma in situ occurred predominantly in the external cervical os and adjacent endocervix. Frequently, the tumor grew as a continuous sheet over large areas of the endocervix. However, in a significant number of cases, the tumor was limited to small foci so that cone biopsy was deemed preferable to punch biopsy because the larger sample of tissue more likely would demonstrate the lesion.

Hysterectomies revealed residual carcinoma in situ in 5 of 22 cases included in the topographic survey and in 17 other cases. This observation demonstrates the necessity of hysterectomy or careful cytologic follow-up whenever a cone biopsy has revealed intraepithelial carcinoma.

Stromal invasion was infrequently demonstrated. There were 2 rare cases of carcinoma in situ with lymphatic invasion. In one, the lymphatic permeation was unusually extensive and there were metastases to regional lymph nodes.

Several histopathologic observations are delineated.

—AUTHORS' SUMMARY

Fanger, H., and Murphy, T. H.: Carcinoma in situ of the uterine cervix. Surg. Gynec. & Obst. 111: 177-182, Aug., 1960.

Tumors of the Venous System

Twenty-four tumors of the venous system were reviewed. Nine of them involved the inferior vena cava, four the saphenous vein, four the femoral vein, one each in the dorsal metatarsal vein, the axillary vein, left antecubital vein, ulnar vein at the wrist, left inferior colic vein, umbilical vein and spermatic plexus. Nine were benign tumors and leiomyomas. Of the 15 malignant tumors, 12 were leiomyosarcomas, one round cell sarcoma, one endothelial sarcoma and one sarcoma of an undifferentiated type. Symptoms, if present, were those related to the pulsatile mass and hence, were usually secondary to pressure, consisting of pain, swelling, edema and evidence of collateral circulation. Location of signs and symptoms varied as to the vein involved. For example, a tumor involving

the upper one third of the inferior vena cava produced a low pulse pressure, paradoxical pulse, electrocardiographic change and an increase in venous pressure. More advanced signs and symptoms—weight loss, anemia, cachexia, etc.—were readily related to metastatic disease. Diagnosis is dependent on suspicion of a pulsatile mass and confirmation by venogram and/or surgical exploration.

Treatment is still surgical removal with the use of autogenous vein grafts, and/or prosthetic replacement devices. Specific measures as used in cardiovascular surgical conditions are indicated, such as anticoagulation. Radiation can be used in patients with advanced metastatic disease or in those who are considered unsafe for surgery because of associated conditions.

Light, H. G.; Peskin, G. W., and Ravdin, I. S.: Primary tumors of the venous system. Cancer 13: 818-824, July-Aug., 1960.

Tumors of the Gastrointestinal Tract

A review of patients seen over a period of 20 years at the University of Maryland Hospital, with smooth muscle tumors of the gastrointestinal tract, reveals little that is characteristic of this tumor. In general, the roentgenologist is more often correct in his diagnosis preoperatively than is the clinician.

Of considerable interest is one patient with an esophageal malignant tumor who had marked regression of his symptoms and in whom there was a profound decrease in tumor size following irradiation. This method of therapy needs further exploration, particularly as a preoperative measure when dealing with large, bulky tumors, and as a measure of palliation.

In general, there is a small number of patients with sarcomatous gastric lesions whose clinical course is acute and fulminating; prompt and extensive resections in these instances are in order.

There is a small group of tumors which occur in the small intestine from which the symptoms of peptic ulcer derive. These must be kept in mind and looked for when the etiology of these symptoms is not found in the stomach or duodenum.

In the malignant lesions of both small intestine and colon, prolonged survival may be obtained when a vigorous surgical effort is made despite incurable spread of the tumor.

The malignant lesions of the rectum have a devastating outlook and require extensive resection by the combined abdominoperineal route.

—Author's Summary

Buxton, R. W.: Smooth muscle tumors of the gastrointestinal tract. Am. Surgeon 26:666-677, Oct., 1960; p. 676.

Radiation Treatment in Mammary Cancer

Eighty-two women with carcinoma of the breast were treated with radiation. Most of the women refused surgery although a few had other medical contraindications to it. Patients were placed in Portman's classification: Stage I, localized disease of the breast; Stage II, breast disease and localized axillary node involvement; Stage III, more manifest involvement of the regional lymphatic nodes with fixation of the nodes; Stage IV, more advanced metastatic disease. The authors compromised by placing some patients in a combined Stage II and III classification. Four Stage I patients were alive after five years, three after eight years and two after 10 years. Of four Stage II patients, three were alive five and 10 years later. Of seven patients classified as Stage II and III, three were alive after five years, two after seven years,

one after eight years and none after 10 years. Of the 35 of Stage III patients, 21 were alive after three years, seven after five years, two after eight and none after 10. Of the 31 patients in Stage IV, all were dead within three years. Although this series is small when compared with series of surgically treated patients, it does suggest that patients in Stage II and III might respond better to radiation treatment. However, for patients in Stage I or in some early Stage II categories, surgery is better since it offers the possibility of permanent cure and eliminates the complications associated with radiation of the breast area.

Hochman, A., and Robinson, E.: Eighty-two cases of mammary cancer treated exclusively with roentgen therapy. Cancer 13:670-673, July-Aug., 1960.

Phaeochromocytoma and Neurofibromatosis (Von Recklinghausen's Disease)

Chapman, Kemp and Taliaferro report on three cases of neurofibromatosis associated with phaeochromocytoma. The former condition is characterized by brown spots (café au lait) of various sizes, vascular nevi, hairy moles and dermal polyps. Multiple tumors of the central nervous system involving both the peripheral nerves and intracranial structures complete the clinical picture. The diagnosis of phaeochromocytoma was confirmed by the use of histamine, phentolamine (Regitine R), and urinary determinations of catechol amines.

Removal of the adrenal tumors, none of which were malignant, resulted in curing the hypertension but had no effect on the dermatological condition.

The report of these three cases brings to 35 the number of reported patients having both conditions. The authors also reported two additional cases of phaeochromocytoma associated with angiomatosis retinae (Von Hippel's disease). The authors further speculate about the possible relationship of tuberous sclerosis, Von Hippel-Lindau's disease, the Sturge-Weber syndrome and multiple neurofibromatosis. The common points being: all are congenital, arise embryologically from the ectoderm and produce lesions which are quite frequently vascular.

The apparent increased clinical association of phaeochromocytoma with the other mentioned diseases can possibly be explained by its similar embryological origin.

Chapman, R. C.; Kemp, V. E., and Taliaferro, I.: Phaeochromocytoma associated with multiple neurofibromatosis and intracranial hemangioma. Am. J. Med. 26:883-890, June, 1959.

Treatment of Cancer of the Testes

In a study of 36 patients with cancer of the testes, one had a seminoma, 13 had embryonal carcinomas (pure or with seminomas), four had teratocarcinomas (with or without embryonal carcinoma and choriocarcinoma, or both, and with or without seminoma), 18 had choriocarcinomas (pure or with either seminoma or embryonal carcinoma, or both). Of the 18 patients with choriocarcinomas, all had elevated urinary chorionic gonadotropin titers. Changing titers have a prognostic import and frequently occur before any demonstrable clinical change.

Therapy consisted of alternating dosages of actinomycin D, amethopterin and chlorambucil (an alkylating agent). Gastrointestinal, dermal and hematological toxic effects may occur with these drugs and will pass away when the drug is stopped. Of the 23 patients treated by this combination, 12 showed substantial improvement, as noted clinically and by laboratory tests. Duration of improvement was from one to 18 months. Of these 12 patients re-

sponding to treatment, seven showed complete or nearly complete disappearance of multiple pulmonary metastases and/or tumor masses. A fall in the gonadotropic level, if previously elevated, accompanied this improvement. Of these seven, three were asymptomatic for nine to 10 months or more, four relapsed within two to seven months. Another form of treatment consisting of chlorambucil plus actinomycin D was administered to nine patients, two of whom responded with tumor regression. The longest duration of remission was 12 months. The use of 6-diazo-5-oxo-L-norleucine with 6-mercaptopurine in eight patients resulted in only one favorable response. This patient who has been in remission for 39 months showed after surgery an elevated chorionic gonadotropin level, which was the only evidence of a tumor. With treatment, it fell to normal. Two patients showed no response to an alkylating agent and 6-diazo-5-oxo-L-norleucine combination. Excluding the seminomas which respond quite well to radiation, the prognosis for cancer of the testes is extremely poor.

Hence, it is recommended that this form of combined therapy (actinomycin D, amethopterin and chlorambucil) should be used in patients suffering from this condition.

Li, M. C.; Whitmore, W. F. Jr.; Golbey, R., and Grabstald, H.: Effects of combined drug therapy on metastatic cancer of the testis. J. A. M. A. 174: 1291-1292, Nov., 1960.

Meningeal Leukemia

Infiltration of the pia-arachnoid or the brain substance by leukemic cells may produce signs of meningeal irritation, increased intracranial pressure, those secondary to focal nervous system involvement, or a combination of these. Electroencephalographic abnormalities are frequently present. Various spinal fluid changes have been noted, including an increased pleocytosis due to the leukemic cells. Meningeal leukemia occurs primarily in children with acute lymphocytic leukemia. This central nervous system involvement may be the presenting signs and symptoms of acute leukemia, and can even be present when there is peripheral hematological remission secondary to treatment. The prognosis is poor; the antimetabolites, being unable to enter the central nervous system, must be given intrathecally. Other measures include use of adrenal steroids administered systemically, whole brain radiation and other general supportive measures.

Shaw, R. K.; Moore, E. W.; Freireich, E. J., and Thomas, L. B.: Meningeal leukemia; a syndrome resulting from increased intracranial pressure in patients with acute leukemia. Neurology 10:823-833, Sept., 1960.

Thorotrast and Cancer

Kligerman, Lattes and Rankow report four cases of maxillary sinus carcinoma. These patients with sinus complaints had thorotrast instillation into the maxillary sinuses 10 to 21 years prior to developing cancer of the respective sinuses. Complaints directly related to sinus disease brought them under medical observation. X rays showed that the radioactive material was still present in the sinuses. Biopsy confirmed the diagnosis of carcinoma. The relationship of radioactive material, thorotrast and carcinoma is discussed. The possible hazard from its continued use in diagnostic studies, involving the brain, liver, spleen, heart and great vessels, body cavities and duct system, e.g., mammary glands, is again raised as it was in 1952 by The Council on Pharmacy and Chemistry of the A.M.A.

Kligerman, M.; Lattes, R., and Rankow, R.: Carcinoma of the maxillary sinus following thorotrast instillation; report of 3 cases. Cancer 13:967-973, Sept.-Oct., 1960.

scientific controls and cancer controls

Medicine as a science faces the unique difficulty inherent in biological experimentation — namely, the controlled experiment. This difficulty is becoming more acute in the face of the hundreds of diagnostic and therapeutic techniques and agents being brought into existence and demanding appraisal and evaluation for possible use in the treatment of patients.

The frequently heard terms, such as double blind tests, prospective and retrospective studies are expressions of the efforts being made to control experiments so that accurate conclusions may be drawn from the data. Such techniques and others provide means for safeguarding scientific objectivity and veracity in medical experiments. When they have not been applied, arguments and controversy flourish and this, in a sense, is a measure of the lack of maturity of medicine as a science.

For example, the difference of opinions concerning the surgical treatment of breast cancer, expressed in the editorials appearing on pp. 26-29 of this journal, points up the urgent need for action to settle this issue. Such controversies will persist and thrive until scientifically controlled experiments are designed to take problems out of the realm of opinion into the area of fact.

Human experimentation is the core of the problem. This challenge has been with us from the beginning, but is now becoming more pressing. We are rapidly approaching the time when organ transplants for cancer may become clinically feasible and hard decisions concerning human experimentation will be necessary. Already, one state is contemplating legislation to permit prisoners who are to be destroyed by the state for crime to volunteer to undergo fatal medical experimentation.

Such drastic solutions to the problem are for the future, if ever. In the meantime, imaginative methods and ingenuity are providing means of hurdling the obstacle of human experimentation. One of these is the prospective study in which large numbers of the population become their own controls, as well as subjects, in the experiment of life itself. A classic example was the prospective statistical study of the American Cancer Society, which conclusively demonstrated a causal relationship between lung cancer and cigarette smoking. A similar study, involving over a million individuals for a six-year period, is now under way to investigate other epidemiological factors in cancer causation.

This form of statistical research is being conducted more and more, and may provide many important answers in the future. Another technique is the cooperative group study method which permits pooling of patients and data, thus creating larger quotas of subjects and controls for a particular study. An outstanding example is the adjunctive cancer chemotherapy study being conducted jointly in this country.

Until such approaches are made to the controversial aspects of cancer, opinions and not facts will be the basis for treatment decisions affecting the life or death of the victims. Only by controlling our experiments and observations can we hope to control cancer.

Roald M. Grant

COMING MEDICAL MEETINGS

Date 1961	Meeting	City
March 6-9	American College of Surgeons, Sectional Meetings for Surgeons and Graduate Nurses Dr. William E. Adams 40 E. Erie St. Chicago 11, Ill.	Philadelphia
March 6-9	New Orleans Graduate Medical Assembly Mrs. Irma B. Sherwood 1430 Tulane Ave. New Orleans 12, La.	New Orleans
March 6-9	Southeastern Surgical Congress Dr. A. H. Letton 340 Boulevard Atlanta 12, Ga.	Miami Beach
March 8-11	Neurosurgical Society of America Dr. Raymond K. Thompson 803 Cathedral Street Baltimore 1, Md.	Boca Raton, Fla.
March 20-22	Dallas Southern Clinical Society 433 Medical Arts Bldg. Dallas, Texas	Dallas
March 20-24	American Surgical Association Dr. W. A. Altemeier Cincinnati General Hosp. Cincinnati 29, Ohio	Boca Raton, Fla.
Apr. 10-12	American Academy of Pediatrics Dr. E. H. Christopherson 1801 Hinman Ave. Evanston, Ill.	Washington, D. C.
Apr. 13-20	American Academy of General Practice Mr. Mac F. Cahal Volker Blvd. at Brookside Kansas City 12, Mo.	Miami Beach
Apr. 21-28	American College of Obstetricians and Gynecologists Mr. Donald F. Richardson 79 W. Monroe St. Chicago 3, Ill.	Miami Beach
Apr. 24-26	American Association for Thoracic Surgery Dr. Hiram T. Langston 308 Carondelet Bldg. 7730 Carondelet Ave. St. Louis 5, Mo.	Philadelphia

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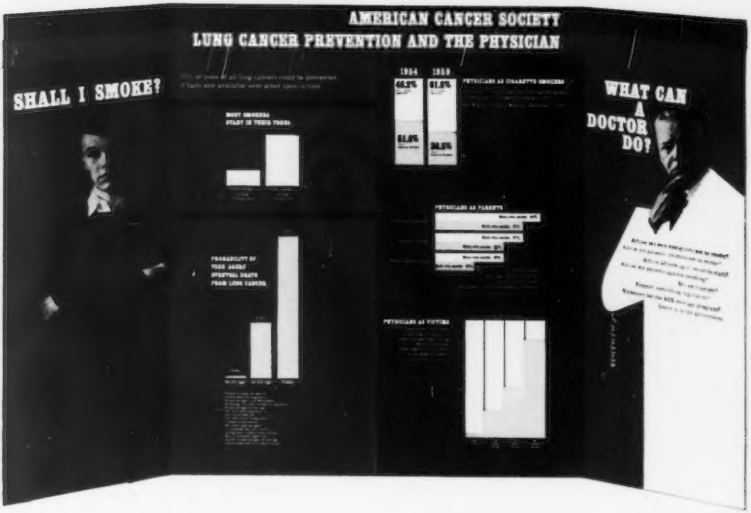

Lung Cancer Prevention and the Physician

Pictured above is an exhibit for the medical profession, entitled "Lung Cancer Prevention and the Physician," which is available on loan through the American Cancer Society Divisions.

Through charts and other illustrative materials the exhibit depicts the high lung cancer death rate today and the projected possible death from this disease of more than one million present school children before they reach the age of 70. The exhibit considers the role of the physician in the prevention of lung cancer. It aims to stimulate physicians' interest in, and support of, the Society's teen-age smoking program.

There are two versions. One is 10 feet in diameter and suitable for state medical society meetings. The other is a 3' x 5' cardboard version which is suitable for staff and tumor conference rooms.